

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Letters Patent of:
Tae-Woong Koo et al.

Patent No.: 7,351,591

Issued: April 1, 2008

For: SURFACE MODIFICATION OF METALS
FOR BIOMOLECULE DETECTION USING
SURFACE ENHANCED RAMAN
SCATTERING (SERS)

**REQUEST FOR CERTIFICATE OF CORRECTION
PURSUANT TO 37 CFR 1.322**

Attention: Certificate of Correction Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Upon reviewing the above-identified patent, Patentee noted typographical errors which should be corrected. A listing of the errors to be corrected is attached.

The typographical errors marked with a "P" on the attached list are not in the application as filed by applicant. Also given on the attached list are the documents from the file history of the subject patent where the correct data can be found.

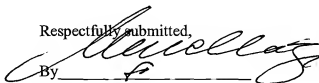
The errors now sought to be corrected are inadvertent typographical errors the correction of which does not involve new matter or require reexamination.

Transmitted herewith is a proposed Certificate of Correction effecting such corrections. Patentee respectfully solicits the granting of the requested Certificate of Correction.

No fee is believed to be due for the filing of this Request. The Commissioner is authorized to charge any deficiency of up to \$300.00 or credit any excess in this fee to Deposit Account No. 04-0100.

Dated: June 25, 2008

Respectfully submitted,



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UNITED STATES PATENT AND TRADEMARK OFFICE CERTIFICATE OF CORRECTION

PATENT NO. : 7,351,591

Page 1 of 1

APPLICATION NO.: 10/814,695

ISSUE DATE : Apr. 1, 2008

INVENTOR(S) : Koo et al.

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In column 12, line 10, in Claim 1, delete "Raman enhancing" and insert - - Raman-enhancing - -, therefor.

In column 12, line 12, in Claim 1, delete "surface modified" and insert - - surface-modified - -, therefor.

In column 14, line 3, in Claim 20, delete "colloid." and insert - - colloid, - -, therefor.

MAILING ADDRESS OF SENDER (Please do not use customer number below):

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This collection of information is required by 37 CFR 1.322, 1.323, and 1.324. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1.0 hour to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Attention Certificate of Corrections Branch, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

DARBY & DARBY

Issued Patent Proofing Form

File#: 2105/80206455-US0

 Note: **P** = USPTO Error

A = Applicant Error

US Serial No.: 10/814,695

US Patent No.: US 7,351,591 B2

Issue Date: Apr. 1, 2008

**Title: SURFACE MODIFICATION OF METALS FOR BIOMOLECULE DETECTION USING SURFACE
ENHANCED RAMAN SCATTERING (SERS)**

S. No.	P/A	Original		Issued Patent		Description of Error
		Page	Line	Column	Line	
1	P	Page 2 Claims (08/07/2007)	Claim 1 Line 6	12	10	In Claim 1, delete "Raman enhancing" and insert - - Raman-enhancing - -, therefor.
2	P	Page 2 Claims (08/07/2007)	Claim 1 Line 7	12	12	In Claim 1, delete "surface modified" and insert - - surface-modified - -, therefor.
3	P	Page 5 Claims (08/07/2007)	Claim 54 Line 8	14	3	In Claim 20, delete "colloid." and insert - - colloid, - -, therefor.

Following the data gathering operation, the data will typically be reported to a data analysis operation. To facilitate the analysis operation, the data obtained by the detection unit will typically be analyzed using a digital computer such as that described above. Typically, the computer will be appropriately programmed for receipt and storage of the data from the detection unit as well as for analysis and reporting of the data gathered.

In certain embodiments of the invention, custom designed software packages may be used to analyze the data obtained from the detection unit. In alternative embodiments of the invention, data analysis may be performed, using an information processing system and publicly available software packages.

The invention will be further understood with reference to the following examples, which are purely exemplary, and should not be taken as limiting the true scope of the present invention as described in the claims.

EXAMPLE 1

Preparation of Silver Colloids

A: To a 250 mL round bottom flask equipped with a stirring bar, was added 100 mL de-ionized water and 0.200 mL of a 0.500 M silver nitrate solution. The flask was shaken to thoroughly mix the solution. 0.136 mL of a 0.500 M sodium citrate solution was then added to the flask using a 200 μ l pipette. The flask was then placed in a heating mantle and the stirrer was set at medium speed. A water cooled condenser was attached to the flask and heating commenced. The heating mantle was applied at maximum voltage, resulting in boiling of the solution between 7 and 10 minutes. Color changes occur within 120 seconds of boiling. The heating is stopped after 60 minutes, the solution is cooled to room temperature and the resulting colloidal suspension is transferred to a 100 mL glass bottle for storage.

B: To a 250 mL Pyrex glass bottle with 100 mL ultrapure water, was added 1. mL of a 0.500M silver nitrate solution. This solution was mixed well prior to addition of 0.5 mL of a 0.500M sodium citrate solution. About 3 grams of PTFE boiling stones (6 mm, VWR) were then placed into the bottle. A cap was placed on the bottle but not screwed tightly, and the bottle was placed in the center of a microwave oven (1350 Watt, Panasonic Model NN-S53BF, Type S333). The heating profile was programmed as follows: P10 (maximum power) for 90 seconds and P2 (20% maximum power) for 3:30 minutes. The solution begins to boil in about 60 seconds and color changes occur at 110-120 seconds. After heating the microwave for 5 minutes, the bottle is immediately removed and transferred to a convection oven set at 95° C. (model MO1440SA, Lindberg/Blue, Ashville, N.C.). The bottle is removed from the convection oven and the final volume of the suspension is adjusted to 100 mL with ultrapure water. A typical Raman spectrum is given in FIG. 1. To compare the Raman enhancement with the best lot obtained from a titration method, the peak height at wave number 1320 cm^{-1} was normalized by that of the best lot from the titration method. Data from several preparations using the microwave method are given in FIG. 2.

Although the invention has been described with reference to the above example, it will be understood that modifications and variations are encompassed within the spirit and scope of the invention. Accordingly, the invention is limited only by the following claims.

What is claimed is:

1. A method for producing a cluster of surface-modified metallic colloid comprising (1) metallic colloid comprising a metal and (2) a Raman-enhancing organic molecule on a surface of the metallic colloid, the method comprising:
 - preparing a solution comprising cations of the metal and a reducing agent by dissolving the cations and the reducing agent in the solution, subsequently heating the solution to produce the metallic colloid, modifying the metallic colloid by attaching the Raman enhancing organic molecule to the surface of the metallic colloid to produce the surface modified metallic colloid, wherein the Raman-enhancing organic molecule comprises a moiety that has an affinity for the metallic colloid and another moiety that has an affinity for a biomolecule, and aggregating a plurality of the surface-modified metallic colloid to form the cluster of surface-modified metallic colloid.
 2. The method of claim 1, wherein the reducing agent is citrate or borohydride.
 3. The method of claim 1, wherein said heating is performed for at least about 30 minutes.
 4. The method of claim 1, wherein said heating is performed for at least about 60 minutes.
 5. The method of claim 1, wherein said heating is performed using microwaves.
 6. The method of claim 1, wherein said heating is performed using a convection oven.
 7. The method of claim 1, wherein the metal is silver, gold, platinum, or aluminum.
 8. The method of claim 1, wherein the Raman-enhancing organic molecule is a bifunctional organic molecule.
 9. The method of claim 1, wherein the Raman-enhancing organic molecule contains sulfur.
 10. The method of claim 1, wherein the Raman-enhancing organic molecule has a molecular weight less than about 500 Daltons.
 11. The method of claim 1, wherein the Raman-enhancing organic molecule contains a thiol moiety or a disulfide moiety.
 12. The method of claim 1, wherein the Raman-enhancing organic molecule is thioamic acid, L-cysteine diethyl ester, S-carboxymethyl-L-cysteine, cystamine, or meso-2,3-dimercaptosuccinic acid.
 13. The method of claim 1, wherein the solution is an aqueous solution.
 14. The method of claim 1, wherein said subsequent heating the solution is performed at a temperature of about 95° C.
 15. The method of claim 1, wherein the metallic colloid produces a higher SERS signal than that produced by another metallic colloid comprising the same metal except that the another metallic colloid is produced by titrating the cations and the reducing agent in the solution at a near boiling point temperature.
 16. The method of claim 15, wherein the metallic colloid produces at least about 50% higher SERS signal than that produced by the another metallic colloid.
 17. The method of claim 1, wherein the cations and reducing agent are each present in the aqueous solution at a concentration of about 0.5 M or higher than 0.5 M.
 18. The method of claim 1, wherein the metallic colloid has a Raman signal that is 50% or more than that of a silver colloid prepared by a titration method wherein a boiling silver nitrate solution is titrated with a sodium citrate solution to produce the silver colloid.

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19. The method of claim 1, wherein the metallic colloid is formed by aggregating a plurality of the metallic particles to form clusters ranging from about 50 nm to 200 nm.

20. A method for producing a cluster of surface-modified metallic colloid comprising (1) metallic colloid comprising a metal and (2) a Raman-enhancing organic molecule on a surface of the metallic colloid, the method comprising:

preparing a solution comprising cations of the metal and a reducing agent by dissolving the cations and the reducing agent in the solution, subsequently heating the solution to produce the metallic colloid, modifying the metallic colloid by attaching the Raman-enhancing organic molecule to the surface of the metallic colloid to produce the surface-modified metallic colloid, wherein the Raman-enhancing organic molecule comprises a moiety that has an affinity for the metallic colloid and another moiety that has an affinity for a biomolecule, and

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aggregating a plurality of the surface-modified metallic colloid to form the cluster of surface-modified metallic colloid, wherein the cluster has a size ranging from about 50 nm to 200 nm.

21. The method of claim 1, wherein the metallic colloid has a Raman signal that is about 140% to 180% more than that of a silver colloid prepared by a titration method wherein a boiling silver nitrate solution is titrated with a sodium citrate solution to produce the silver colloid.

22. The method of claim 1, wherein the cluster of surface-modified metallic colloid has a Raman signal that is greater than that of a silver colloid prepared by a titration method wherein a boiling silver nitrate solution is titrated with a sodium citrate solution to produce the silver colloid.

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